

Dercum (F.X.)

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in the Nervous System.*

BY

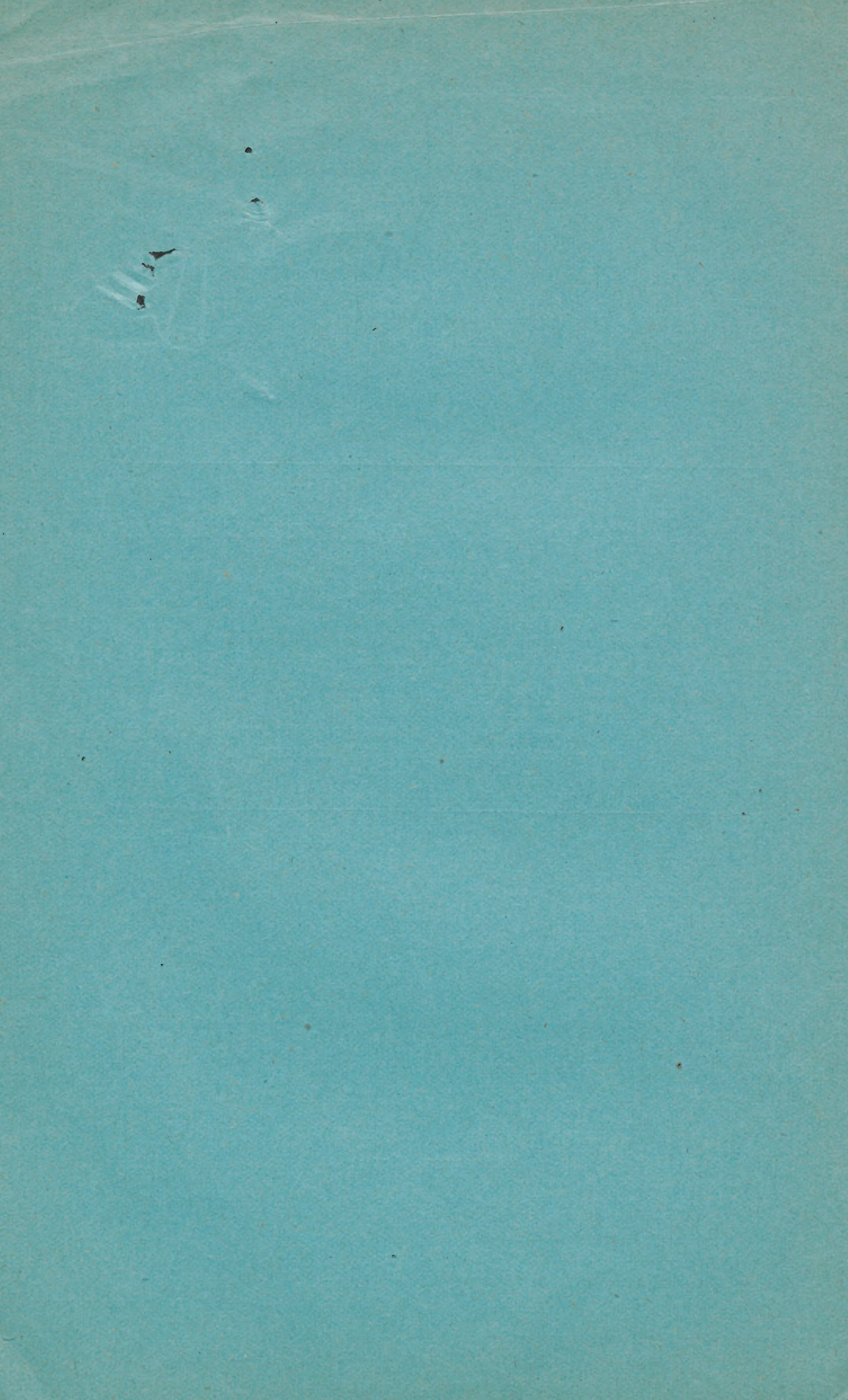
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FROM

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES,
SEPTEMBER, 1894.



THE THERAPEUTICS OF INFECTIOUS PROCESSES IN THE NERVOUS SYSTEM.¹

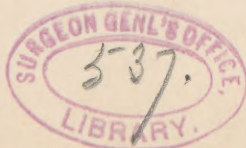
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A CONSIDERATION of the treatment of infectious nervous processes involves not only the treatment after infection has occurred but also its prevention. The latter is not the least important part of our subject, and to it we will first give our attention.

From much that we know we have reason to believe that the occurrence of infection is markedly influenced by the nervous system. Charlin and Ruffer, in experiments on animals, discovered that section of the sciatic nerve under certain conditions favored pyocyanic infection. Roger cut the sympathetic nerve in the neck, and saw erysipelas which he had inoculated into the ear of the same side disappear, while on the other side it continued to develop. In another instance, instead of the sympathetic this investigator cut the auriculo-temporal nerve, when the reverse result was observed, for the streptococcus developed more readily on the side of the section. Not only did he prove that the nerves influence the process, but that different sections produced different results. Startling as are these facts, they are, after all, in harmony with what we know of the control which the nervous system exercises over all of the functions of the economy. Not only does it dominate digestion, circulation, and nutrition in general, but also absorption. The vasomotor nerves, through their influence on the size of the vessels and probably on the size of the stomata of the capillaries, are a powerful factor in determining the result. It is probable that the destructive inroads of germs are at times favored and at other times delayed or prevented by their action. Thus when the vessels are constricted and small it is probable that invasion can take place with little or no interference on the part of the organism. On the other hand, if the vessels be in their normal condition or perhaps a little dilated, it is probable that the white blood-corpuscles pass out into the surrounding tissue and act as phagocytes upon the invading germs, and that, in addition, the liquid constituents of the blood exert an action both bactericidal and antitoxic.

¹ Third paper in the discussion on "The Influence of Infectious Processes on the Nervous System," before the General Session of the Congress of American Physicians and Surgeons, June 1, 1894.



If the rôle of the nervous system is so important, if the ingress of microbes is to so great an extent under nervous control, prophylaxis assumes an importance altogether peculiar. It becomes at once evident that our ability to resist infection depends largely upon the maintenance of a normal nervous tone—*i. e.*, nervous health. Indeed, we may here find a partial explanation of the difference of susceptibility displayed by persons exposed to infection under similar circumstances. That these thoughts are not mere speculative fancies is proven by such experiments as those of Charrin and Roger on the rôle which fatigue plays on the evolution of infection. These experimenters constructed an apparatus, on the principle of the squirrel-wheel, by means of which they brought about marked muscular fatigue in animals. They conclusively proved that this fatigue distinctly favored the development of infection. Thus, in one series of their experiments they used thirty-six rats; of these they reserved fifteen as control animals. Twenty-one they inoculated with the germs of charbon, and then by means of their apparatus caused them to walk for from two to eight hours daily for three days in succession. It was found that the resistance of the animals to inoculation varied according to age and size. In each series of experiments the investigators were careful to employ specimens of nearly equal size, taking care to preserve one, if any the smallest, as a control animal. All were inoculated into the skin of the flank. Three of the control animals withstood perfectly nine drops of the virus. The same dose was administered to eight others who were then subjected to the fatigue test. One of these resisted the inoculation fully, a second died at the end of four days, four at the end of three days, and two on the day after the inoculation. By increasing the dose, the experimenters were able to kill one of the control animals, but the latter did not die until at the end of five days. Further studies made by them yielded the same results, and in every instance, both by microscope and cultures, they verified the cause of death. The bacteria were always discovered in the blood. By their experiments they were also led to believe that fatigue favors infection from the intestinal tract. The conclusions to be derived from these researches are so clear as to be self-evident.

We have learned from the investigations of Hodge that nerve cells undergo certain changes in the course of their functional activity and that these changes can only be interpreted as those of fatigue. When analyzed they resolve themselves into simple loss of substance. That there may be in addition other changes less tangible—changes which are attended by the formation of products the result of retrograde metamorphosis—is also probable. However, the simple story of the tissue waste teaches us a fact of great significance, for loss of substance being synonymous with fatigue, it must also be taken as synonymous with

weakness, and, in virtue of the rôle that the nervous system seems to play in infection, this weakness must be construed as synonymous with a diminished power of resistance to the invasion of germs. The first problem, therefore, that presents itself is the prevention, if I may be permitted to so state it, of undue waste of nervous substance through undue or excessive fatigue. To repeat what is known to every physician, that long-continued overwork, with insufficient rest and food, favor the development of various diseases, may seem unnecessary here, but that we are now in a position to frame an intelligent hypothesis based upon the experiments of Hodge, Charrin and Roger, and others, is certainly interesting and important. The value or rather the absolute necessity of a proper proportion of sleep and a proper amount of food follow as unavoidable corollaries, but another element must also be considered. It not only suffices that the nerve cell should have rest and that sufficient pabulum for its regeneration should be at hand, but, to repeat what is universally known, exercise both mental and physical within physiological limits is absolutely necessary. The solution, therefore, of the question of a proper prophylaxis is answered thus far by a proper proportion of food, rest, and exercise. The nervous health is, of course, influenced by numerous other factors concerned in general hygiene and special etiology; but these, I take it, do not directly concern us here. Simple as the conclusions with regard to general prophylaxis appear, their value must not be underestimated. To realize that overwork leads not only to nervous exhaustion, a fact with which the laity are as familiar as ourselves, but that it also opens the avenues of infection, is one which should be appreciated in its broadest significance.

The question next arises: "Are there any means of *special* prophylaxis against this or that infectious nervous disease?" Here, unfortunately, the answer which we can give is hesitating and clouded with uncertainty. At once the preventive inoculations of Pasteur, Behring, and Tizzoni and Cattani, suggest themselves, but at the same instant doubts as to the advisability and applicability of the methods arise. Roughly speaking, the question of preventive inoculation for infectious nervous diseases must be answered, as we shall see farther on, in the negative. However, special prophylaxis appeals to us from another quarter. Supposing that the general economy is already the subject of bacterial infection, are there no means by which the spread of the infection to the nervous system can be averted or the chances for such infection diminished? Is there anything that can be done in the various infectious fevers, in general pyæmia, in suppurative otitis media, in lung abscess, empyema, etc., to prevent nervous involvement? Are there any means by which the meningitis, brain abscess, and neuritis, that every now and then make their appearance in the course of these diseases, can be prevented or the chances of their occurrence lessened?

With regard to abscess, the question may often be answered in the affirmative, but at times the involvement of membranes, centres, or nerves is to be explained either by the excessive virulence of the infection or by the special susceptibility of the nervous system to the poison in question. At times, too, secondary involvement of the nervous system is to be regarded as related to the sudden suppression of some local symptom, as a purulent discharge or perhaps an eruption.

Where the nervous system is threatened by the existence in other structures of foci of infection, abscesses, and suppurating cavities, such as purulent otitis, mastoid disease, purulent inflammation of the frontal sinuses or of the orbit, lung abscesses, empyema, the indications as to prophylaxis are very clear. A suppurating cavity, be it large or be it small, constitutes a perpetual danger, and the importance of securing free evacuation and free drainage, wherever such a cavity is situated, need not here be dwelt upon.

Practically, we must admit, questions of general and special prophylaxis are presented to the physician far less frequently than questions of treatment after infection has actually occurred. Here the problem again resolves itself into general and special methods. The general indications are of course clear. They are: first, to arrest or limit the infective process; and, secondly, to bring about a rapid elimination of morbid products, toxines, etc., or the evacuation of tissue detritus, such as we find in purulent inflammations, abscesses, and the like. The first indication, namely, to arrest the infective process, is easier proposed than carried out. Unhappily we are not yet possessed of a germicide which will enable us to bring about the death of germs within the nervous system without injury to the tissues. Such a substance would be one that would act upon microbes as quinine appears to act upon the organisms of Laveran. It is in this field that chemistry and the biological laboratory may some day yield us a great discovery.

In the meantime Pasteur, Koch, Behring, Kitasato, Tizzoni and Cattani, and others have attempted the solution of the problem on an entirely different basis. The familiar fact that the growth and multiplication of the torula is arrested by the very alcohol to which it gives rise, seems first to have suggested the attempt to combat the infectious microbes by the toxines which they themselves produce. However, with the possible exceptions of tuberculosis and leprosy, the symptoms produced by infectious micro-organisms appear to be due not so much to the germs as to these very toxines. Notwithstanding, these attempts have led to very interesting and in some instances very valuable results, and these we will briefly review.

As regards tuberculosis the story of the hopes and failures of Koch's lymph is too recent to bear repetition. In tuberculosis of the nervous system the lymph is shown to be not only useless but even dangerous.

This is the experience of Brehm and others in tuberculous meningitis, and even if it be given for tuberculosis of other structures tuberculous meningitis may arise during its use. Caspersohn, for instance, observed such meningitis develop while he was treating his patient for tuberculous fistula and abscess of the right thigh and hip.

In the treatment of leprosy by the lymph, failure appears to have been almost equally marked. The writer has collected in all sixty-four cases treated by Koch's lymph in 1891. Not a single cure was reported among them all. Poupinel noted considerable improvement in two cases out of five. Kaliendero and Babès noted amelioration and improvement of general condition in eleven. Schwartz noted improvement in a number out of twenty-two cases, but did not follow them up. Goldschmidt noted improvement in one out of ten. It appears that even these general statements of amelioration and improvement must be taken with considerable allowance. Danielssen, after having treated fourteen cases, comes to the following conclusions: First, that there is a local and constitutional reaction which comes on from four hours to three days after the injection of the lymph. The local reaction occurs later. Second, that the reaction has no favorable influence upon the leprosy trouble, but on the contrary it aggravates the latter. Third, that the tuberculin does not destroy the lepra bacillus, but that it fertilizes the soil for the latter, the bacilli increasing in activity and destructive qualities more than if the patient had received no treatment. Finally he concludes that the method can produce a kind of immunity when the tuberculin is used for a long time, but that the method does not arrest the progress of the disease, for new symptoms may develop under its use. Whether modifications of the lymph or such methods of preparation will yet be devised as will eliminate all elements of danger, and whether it will finally be successful, can of course only be conjectured.

When we turn our attention to Pasteur's efforts with hydrophobia the story is decidedly more encouraging. It is obviously out of place here, nor would time permit us, to go into a detailed discussion of Pasteur's methods, nor to consider in detail the claims and criticisms of his practical results. However, a brief review of his methods is necessary for our purpose. As is well known, Pasteur found that if the spinal cords of rabbits inoculated with rabies are kept in a room with a constant temperature of 20° C. (68° F.), they gradually lose their virulence with each day's action of the dry atmosphere and the surrounding temperature until, after the expiration of fourteen days, a material remains which produces no perceptible action upon rabbits or dogs when introduced into the brain. It does, however, protect the animal against future inoculations with most active forms of the virus. It appears that the process of drying destroys the germ (whatever that may be),

but leaves the toxine produced by the germ practically unchanged. Pasteur obtained his virus by inoculating rabbits beneath the dura mater with the spinal cord of the rabid dog. Then, this rabbit having developed rabies, its spinal cord is inoculated into a second rabbit, and this process is repeated until finally it is found that the virulence has increased to such an extent that a small particle of the cord injected into a rabbit will kill in seven days. The spinal cord of the last animal is then attenuated in dry air as described above. A small fragment of this material is then diluted in sterilized bouillon. These injections are repeated with material obtained from cords of greater virulence until finally a very virulent material is injected, when the animal is found to be immune. Pasteur applied his method to the treatment of patients suffering from the bites of rabid animals, by beginning with material obtained from cords that had been dried for a period of fourteen days and by steadily following the initial injection with material obtained from cords of less attenuation until at last the cord of one day's drying was used. The injections were made under the skin. The theory of Pasteur is that a gradual accommodation of the organism to the virus occurs.

As is well known, Pasteur's claims were confirmed by the English Committee of Investigation. This committee reported that the experiments of Mr. Horsley entirely confirmed Pasteur's discovery of a method by which animals may be entirely protected from the infection of rabies; and further, that the personal investigation of Pasteur's cases by members of the committee was, so far as it went, entirely satisfactory, and convinced them of the perfect accuracy of his records. Among those who have also given attention to the question of hydrophobia experimentally must be mentioned Tizzoni and Cattani. These investigators experimented with the vaccine extracted from the central nervous system of rabbits dying from fixed virus, though even a vaccine prepared from the first generation after inoculation gave positive results. Ten cubic centimetres of their liquid contains dissolved the active principle of about one gramme of rabic nervous system. This solution failed absolutely to produce rabies by experimentation, and was entirely aseptic. With this liquid they succeeded in making twelve out of fourteen rabbits entirely immune. In the two in which preventive inoculation had been unsuccessful the quantity administered seemed to have been insufficient. Tizzoni and Cattani concluded that one inoculation is sufficient, and that even on the following day the animal may be inoculated with rabic virus without developing the disease. They further proved that their vaccine was efficacious even when administered during the incubation period of rabies, though a larger dose is in such a case necessary. They concluded, however, that in the case of rabbits the treatment must not begin later than four days after the infection.

More recently Tizzoni and Cattani made the interesting discovery

that in sheep and dogs which had been injected under the dura mater with rabic nervous system the serum acquired an anti-rabic value. This anti-rabic quality increases in intensity until the twenty-fifth day after vaccination—that is, subdural inoculation—and then begins to decrease. This is the time when the serum should be removed from the animal. The serum, they claim, produces no unpleasant effects whatever and is absolutely lacking in virulence. These interesting and original observations are in harmony with those made previously by them regarding the immunizing and therapeutic effects of the serum of rabbits that had been rendered immune by vaccination with the rabic virus. The scientific importance and wide significance of these discoveries cannot be overestimated.

The story of the extensive application of Pasteur's methods, his extravagant claims as to results, together with the active opposition they aroused in certain quarters, is still too recent to bear repetition. In Paris itself his claims, as is well known, have been actively combated by Lutaud, who showed that in France over a period of twenty-three years (1850 to 1872) there were but 685 deaths from rabies—that is, about 30 a year. Pasteur claims that during the five years 1881 to 1885, there were 60 deaths in the hospitals of Paris. This is disputed by Lutaud, who cites cases with the hospitals at which they were treated, showing only 26 deaths. Again, Pasteur claims that the annual mortality for seven years up to 1870 is 76; Lutaud proves it to be 47.7. Vulpian states, in Pasteur's name, that the number of persons bitten by rabid dogs in one year was 100 and the number of deaths 16, and that these occurred in persons not treated by the Pasteur method. He then follows this statement by saying that out of the 1726 cases treated only 12 died in place of the 276 who would otherwise have died without treatment. Lutaud called attention to the remarkable increase of the number of cases of rabies implied by these statistics. Pasteur says that of 1929 Frenchmen treated 18 died up to December 31, 1886; all told there were 2682 cases of hydrophobia. Lutaud then shows that the cases of death in the Pasteur Institute during the year 1886 numbered 22, and further that there were also 17 deaths without treatment, making a total of 39 deaths for the year 1886, which is an excess over the mean annual mortality of previous years, which was 30. From 1886 to 1890 there were 90 deaths after Pasteur's treatment had been employed. The cases, names, addresses, etc., are recorded. If we add to this the number of deaths of those not treated, we have the figures 154, a mean of 38 deaths a year.

Among the opponents of Pasteur's methods must also be mentioned Dulles, whose criticisms have been exceptionally severe, as the following citation from a paper read before the recent meeting of the State Medical Society of Pennsylvania will show:

"The number of cases of hydrophobia that occur in this country is happily small. It would doubtless be smaller still but for the exploitation of the Pasteur Institute conducted by Gibier in New York, and of its feeble imitator conducted by Lagorio in Chicago. These institutions and the newspapers that, in times past, have published sensational accounts of cases of so-called hydrophobia, have in a mild way reproduced some of the conditions which make France the hotbed of hydrophobia as well as of hystero-epilepsy. But the psychological make-up of Americans is less favorable to the development of the germs of hydrophobia or those of hystero-epilepsy than is that of the French, and consequently there is less of either here than there is in France. There the history of the last six years differs but little from that which I described to you in my last report. As then, so now, the number of deaths in France is greater than it was before Pasteur, just ten years ago (in May, 1884), boasted to a newspaper reporter: 'Whoever gets bitten by a mad dog has only to submit to my three little inoculations, and he need not have the slightest fear of hydrophobia.' The year before he made that boast there were 4 deaths from hydrophobia in Paris (the department of the Seine); the year after, when he had practised his preventive method for six months, the deaths from hydrophobia leaped at once from 4 to 22. In 1886 the number fell to 3 again in Paris; but I have a list of 23 persons that died after treatment by Pasteur himself in that year. In 1887 the deaths in Paris rose to 9, in 1888 to 19. These oscillations indicate that Pasteur's method is no more preventive of hydrophobia than is the method which he declared, in 1884, would eradicate rabies in dogs. On the contrary, Pasteur's method has undoubtedly increased the number of deaths from hydrophobia. I have indicated what has taken place in France and can assure you that there has been no diminution of the number of deaths from hydrophobia in any part of the world since Pasteur's infallible cures were inaugurated; and at the same time there has been added to these a large number of deaths due to inoculations with virus of what ought to be called 'Pasteur's disease.' Just how many these have been, no man can say. The statistics in regard to these deaths are confusing. Those from friendly sources contain remarkable discrepancies. Pasteur's own statistics, published in the *Annales de l'Institut Pasteur* for March of this year, admit 72 deaths in seven and one-half years after treatment in Paris. My own statistics show a much larger number, while I find that Dujardin-Beaumetz, an enthusiastic supporter of Pasteur, reported to the Académie de Médecine on June 21, 1892, 98 cases in only six years, which is just 26 cases more than Pasteur himself reported for eight years. One way in which such curious figures appear may be seen when we examine Pasteur's detailed report for 1893, when we find that 10 actual deaths are set down as 4, because 2 of the 10 unfortunates succumbed in less than fifteen days, 3 developed their fatal disease while receiving the inoculations, and only 1 did not stay to have the treatment completed. The same manipulation may be found in the reports for other years."

In the limited time at our disposal a detailed review of the evidence pro and con of Pasteurism and hydrophobia is impossible. However, it is vain to deny the truth of Pasteur's experimental researches upon animals, while the evidence as regards human beings is in *specific* instances strong and convincing. It goes without saying that of the number of dogs who inflict bites upon human beings a percentage only are rabid, and finally, that of the number of persons bitten by rabid dogs only a portion become infected with the disease. The publication of Pasteur's methods, the wide distribution among the laity of information concerning his treatment, and the well-known predisposition of the French to hysteria, have increased enormously the number of persons who have directed medical attention to bites received by them, and in

this way is doubtless to be explained the enormous increase in the number of cases.

However, in a disease the mortality of which untreated is practically 100 per cent., any method of treatment that yields even a ray of hope deserves trial. Inasmuch as the period of incubation is generally prolonged, there is certainly time for giving a patient the benefit of Pasteur's method. It would seem that the rational course in a given case would be to remove the spinal cord of the supposed rabid dog, and to perform with it test inoculations upon rabbits, and having determined the actual existence of rabies by this means, to rapidly prepare attenuated material. The evidence shows that the risk involved by the injection of such material is exceedingly small. Let us hope that the discovery of Tizzoni and Cattani, of the anti-rabic value of the serum of dogs and sheep upon which subdural inoculations have been practised, will lead to a simpler and more direct method.

When we turn our attention to the subject of tetanus we find the existing state of investigation to be more interesting still. In 1890, Kitasato attempted to make animals immune to this disease. His attempts by means of repeated inoculations of attenuated virus failed to yield a satisfactory result. However, by applying the method which Behring had devised in experiments with diphtheria, he finally succeeded. He first injected a middle-sized rabbit with 0.3 cubic centimetre of the filtrate of tetanus culture subcutaneously. Immediately afterward he injected into the same area 3 cubic centimetres of a one per cent. solution of iodine trichloride. In twenty-four hours the same dose of iodine trichloride was again administered. In forty-eight hours some symptoms of tetanus infection having appeared, the dose of iodine trichloride was again repeated, and twice thereafter; in all, five doses were administered before tetanic symptoms finally disappeared. The animal was entirely well in ten days. On the fourteenth, eighteenth, and twenty-fifth days large doses, 2 to 3 cubic centimetres, of tetanus culture were administered with negative results. Two control animals which received but a moderate dose of the culture, died in a few days. This method was successful in producing immunity in 40 per cent. of the animals experimented upon, and further, this immunity persists for two months. Experiments were further made to render other animals immune with the blood of immunized rabbits. Kitasato injected liquid blood, before coagulation, into the abdominal cavity of mice, who, with control animals, were subsequently inoculated with tetanus bacilli, and in such a dose that the control animals died in thirty-six hours; the others remained immune. The serum also revealed therapeutic properties. An animal could be infected with tetanus, and after symptoms had appeared, successful results were obtained by injecting the serum into the abdominal cavity. He further proved that when the filtrate of tetanus culture is

mixed with the serum of the tetanus-immune rabbit, it fails to kill the mice, while control animals perish. Behring also experimented extensively in the same field, and found that iodine trichloride added to his carbolized tetanus culture in increasing doses, made the culture less and less virulent, and finally innocuous. Rabbits which survived injections of this mixture were able to stand more than the minimal dose necessary to kill control animals, and thus attained a certain degree of immunity which, through further inoculation with culture-fluid, became greater and greater. Behring also, and Schuetz later, demonstrated the possibility of thus immunizing horses and sheep.

More interesting than all, however, are the combined researches of Brieger, Kitasato, and Wassermann. To begin with, they noted that when they attempted to grow the tetanus bacillus in a watery infusion of thymus gland, they were only occasionally successful. They then made the remarkable observation that the tetanus bacillus, though it grew, failed utterly to develop spores. Even when they submitted the cultures to the incubator for as long a period as fourteen days, the result did not vary. However, when these sporeless bacilli were transferred to other culture media they again developed spores. That is, the tetanus bacillus simply loses the power of spore-bearing while in the thymus infusion. These investigators then followed up this discovery by inoculating animals with cultures made in thymus infusion, with the result that they were able to produce immunity in all of the animals experimented upon. While the trichloride method yielded 40 per cent. of immunized animals with the immunity persisting for two months, the thymus method yielded immunity in 100 per cent., and at the end of four months this immunity was as marked as ever.

Behring, Frank, Kitasato, and Tizzoni and Cattani were successful in conferring immunity upon other animals by the injection of immunized serum. They all demonstrated also that this serum possessed in addition curative properties; that is, animals in which tetanus had been produced by inoculation, and which were afterward treated by injections of immunized serum, recovered, while control animals perished. Further, they all found that the dose required to bring about a cure was far greater than that necessary to bring about immunity. The practical application of these striking and brilliant results in the cure of tetanus in man, possesses an interest that is altogether peculiar. In a disease, the mortality of which is variously estimated at from 75 to 90 per cent., being second only to hydrophobia, the introduction of a really successful plan of treatment would rank as one of the greatest achievements of modern medicine.

Inasmuch as the quantity of serum which could be derived from mice and rabbits was obviously too small to be available in man, Behring experimented upon horses and sheep. Even under these circumstances

it seemed at first as though the quantity of serum required would be too large to be practicable. However, it was found that the serum of the immunized animals increased in strength with time, and Behring finally succeeded in immunizing the serum of horses until it attained an immunizing value of 1 to 1,000,000 body-weight. Of this serum one gramme will be sufficient to immunize 1000 animals of 1000 grammes body-weight each, against a minimal fatal dose of tetanus culture.

According to Behring and Frank, and also Tizzoni and Cattani, the healing value of the serum is 1000 to 2000 times less than its immunizing value. Therefore a serum which has an immunizing value of 1 to 1,000,000 would have a curative value of only 1 to 1000. That is, for every kilogramme of body-weight one gramme of serum should be used. Again, in cases in which the disease has already advanced, or in which the infection has already produced severe symptoms, a still larger quantity must be employed. It was a serum of this strength that was applied by Rotter in the treatment of a case of tetanus in man. The patient was a male, twenty-five years of age, who had developed tetanus after a wound of the hand. The first injection was not made until seven days after the appearance of trismus. 66 grammes of immunized horse-serum, containing 0.5 per cent. of carbolic acid, were injected into four places beneath the skin of the back. On the day following, his condition remained unchanged. A second injection of 50 grammes of the same serum was now administered. The seat of the injection was the left pectoral region, the needle being turned in different directions. The pain caused was slight. On the following day the patient expressed himself as feeling decidedly better. Trismus and rigidity of the back of the neck and of the legs were somewhat lessened, though not markedly so. Twitching ceased. 45 grammes of serum were now administered into the left Mohrenheim fossa. No reaction was noticed at the punctures or area of the injections. Distinct improvement was noticed on the following day in all of the symptoms. The fourth and fifth injections were then administered on successive days. The symptoms now steadily improved, though slowly. On the seventeenth day, after the last injection, the patient was dismissed from the hospital, with a slight rigidity of the left forearm, which five days later entirely disappeared.

Another interesting case reported is that of Moritz. Behring had succeeded in bringing up the immunity of the serum of a horse to so high a value that it was estimated to have an equivalence of 1 to 10,000,000—that is, 1 cubic centimetre would be equivalent to rendering immune 500,000 mice of 20 grammes each, or 143 human beings of 70 kilogrammes each, against a minimal fatal dose of the tetanus poisoning. These figures seem almost incredible.

It was such a serum that Moritz used in a boy twelve years of age. Unlike Rotter's case, the attack of tetanus did not follow a trauma. One

week after the appearance of trismus 20 c.c. of an immunized serum were injected into the inner side of the left thigh, while 10 c.c. were injected into the corresponding portion of the right thigh, and 20 c.c. into Mohrenheim's fossa. The next day 30 c.c. additional were injected, while on the day following, 15 c.c. more were given—in all, 95 c.c. By this time such decided improvement had set in that the injections were discontinued. Three weeks after the beginning of the treatment the boy was able to walk, and some ten days later resumed his school.

In Italy this method of treatment has been employed in quite a number of cases, as many as twelve having been thus far reported. Tizzoni and Cattani, from their experiments, came to the conclusion that for practical purposes in man, when the strength of the serum has reached 1 to 1,000,000 it is most fit for use, and that the value of the serum depends only on the amount of the antitoxine it contains and not upon its origin—that is, not upon the particular animal from which it is derived. It would be unnecessary, therefore, in a case of urgency to wait until increasing injections had afforded a maximum intensity to the serum, but to at once ascertain the strength of the latter and then to administer it in a proportionate dose.

These investigators also showed that the alcoholic precipitate derived from the serum is of the same value as the serum itself; though Behring maintains that the antitoxine does not exist in Tizzoni and Cattani's dry powder in its purity. Behring also estimates the value of Tizzoni's antitoxine as but 1 to 10,000. It would, therefore, have a far lower value than that of Behring's serum. Tizzoni estimates that of his serum, 70 c.c. would be the dose for a case of moderate severity in man in the beginning. At a later stage, 210 c.c. would be required. This would equal of the alcoholic precipitate 5 to 6 centigrammes in the first instance and 10 to 12 grammes in the latter.

The writer has collected in all some thirty-four cases of tetanus of various origins, treated either by the powder of Tizzoni or by the immunized serum. Of these, twenty were successful; certainly a large proportion. However, it is not improbable that in some of these cases the recovery was brought about not only by the antitoxine employed, but also by other measures, *e. g.*, amputation or early active treatment of the wound. Further, in the majority of the Italian cases the period of incubation was relatively long and the cases, as a whole, seemed of a mild type. Certainly they were neither very acute nor very severe. Rotter in his criticism of the first eight Italian cases goes so far, indeed, as to maintain that not one of them taken alone can be considered as proving the curative properties of Tizzoni's antitoxine. Finally, it is to be feared that in the long list of successful cases reported, the unsuccessful ones have been most unwisely omitted. If this suspicion be incorrect, the twelve Italian cases, notwithstanding their mild character, constitute

a strong argument in favor of Tizzoni's antitoxine. A number of successful as well as unsuccessful cases have also been reported in Germany and France. Thus Roux and Vailiard were successful in two cases, unsuccessful in five; Renon was unsuccessful in two; Escherich successful in one, unsuccessful in three; Range lost two; Baginsky and Kitasato lost one; Schwartz another. The unsuccessful cases appear to be as much open to criticism as the successful ones. In some the treatment was begun too late, in others an insufficient dose seems to have been administered; in others still, the serum appears to have been insufficient in intensity. In the successful cases the symptoms are never abruptly arrested but disappear slowly, the case often running a prolonged course.

Various speculations have been advanced regarding the method of action of the antitoxine. Tizzoni and Cattani, for instance, believe that the treatment does not so much affect the symptoms that are already present as that it limits the spread of the disease by immunizing or protecting the portions of the nervous system not already affected; that for this reason it has little or no influence on the symptoms already developed. Thus they proved that when the injections of tetanus culture exceeded a certain amount, or the symptoms had widely progressed, the serum was insufficient to cure.

It is, however, extremely probable that the antitoxine possesses the property of directly destroying the tetanus poison. This is the position assumed by Behring. It is difficult to reconcile the theory of immunity with any other hypothesis. A statement of practical, even if of negative importance should be added, and that is that there exists no contra-indication to the use of the serum or of the antitoxine. Its employment appears to be in no way injurious. While the evidence regarding its actual therapeutic value is unfortunately inconclusive, it is still to be hoped that further trial will yield a decisive answer. The promise held out is so great that it not only justifies but absolutely demands this further trial. We learn from Behring that the serum can very readily be preserved by the addition of 0.5 per cent. of carbolic acid, while Tizzoni's results show that in the form of a dry powder it retains its virtues for a long time, and it is not improbable that the methods of preservation will yet be so far perfected that, like other remedies, they can be preserved for long periods and used at will.

The methods indicated by the researches of Pasteur, Koch, Behring, and Tizzoni are not apparently to be limited to the diseases we have thus far discussed, for from Behring we receive the hope that they may also be applied to the treatment of diseases due to streptococcus infection. When we contrast these methods, based as they are upon scientific investigation and deduction, even when we examine most critically the practical results, we realize that the hope they offer of a final conquest of these terrible diseases is nothing less than sublime.

The various other means at our disposal for combating infectious nervous processes resolve themselves into general remedies, drugs, and surgical procedures. It would obviously be out of place before an audience of this character to review well-established and well-recognized principles of treatment pursued in the various infectious nervous diseases, and I deem it my province here to touch simply here and there upon that which may be new. Unfortunately, little that is new can be said under any of these heads. Cold has been applied with varying success, as is well known, in meningitis, both cerebral and spinal, though one of the later writers (Brehmer) saw ill effects follow its use in children. Heat also has a comparatively limited application; Horsley proved experimentally that in hydrophobia it is worse than useless. Baths are rarely employed in infectious nervous diseases. It is not improbable that they would prove of benefit. From the remarkable results of the Brand method in typhoid fever the question arises whether the therapeutic result is due only to the falling temperature, or perhaps to some other action of the water, and it has occurred to me that in such affections as tetanus and cerebro-spinal meningitis repeated and prolonged immersion in water of suitable temperature would be a justifiable expedient. Whether by this means the elimination of toxins would be favored, is a matter that can at present only be conjectured. It is interesting in this connection to note that T. J. Bennett, of Texas, reports a successful case of tetanus cured by frequent immersion in hot baths of from thirty to sixty minutes' duration.

When we turn our thoughts to treatment by drugs we meet little that is either encouraging or gratifying. For hydrophobia the treatment by drugs is equivalent to zero, and for tuberculosis of nervous structures their value cannot be said to be any greater. As regards tetanus, to the various drugs, bromide, chloral, morphine, and the other sedatives that are so familiar to us, a long list, self-condemnatory by very reason of its length, is constantly being added day by day. It includes such drugs as carbolic acid, eserine, strychnine, salicin, pilocarpine, aconite, antipyrine, and even the poison of the rattlesnake.

As regards leprosy, benefit is said to have followed the use of gurjun and of chaulmoogra oil used internally and externally. Chlorate of potash in almost toxic doses is said also to have been followed by good results. Euophen yielded benefit in one case and proved useless in four others. As regards chorea, which, though not demonstrably infectious, is probably so, quinine has recently been advanced by H. C. Wood as possessing unusual value. Extensive trial has, however, shown that it remains secondary in value to arsenic. Antipyrin has also its advocates, and especially is this true of exalgine, which Dana thinks has a specific influence in Sydenham's chorea.

On the whole, the literature affords little that is new on the treatment of infectious nervous diseases by drugs.

Surgical procedures enable us every now and then to accomplish definite and often brilliant results. This is especially true with regard to the evacuation of pus in positions that were formerly deemed inaccessible, *e. g.*, brain abscess, which is no longer the frightful and hopeless disease of former times. Indeed, it now constitutes, to use Macewen's words, "one of the most hopeful of all cerebral affections." It is earnestly to be wished that some surgeon will yet devise a means for the successful treatment of infectious diseases of the various membranes. Certainly, from what we know of their hopeless nature, purulent inflammations would justify even extraordinary procedures. In keeping with these thoughts, C. A. Morton tapped the arachnoid space in four cases of tuberculous meningitis and noted slight improvement in two of them, and Wallace, Ord, and Waterhouse trephined through the cerebellar fossa of a child of five years. A small quantity of fluid escaped, a drainage tube was inserted, and the child did well. In tetanus, also, surgical interference has proved of great value in regard, of course, to the thorough antiseptic treatment of the wound, to excision, and to amputation.

In closing my part of the discussion—a part which I fear has been anything but satisfactory—I desire to make a suggestion in reference to the treatment of tetanus which may be of value. It will be remembered that Brieger, Kitasato, and Wassermann discovered that the tetanus bacillus, though it grew in thymus infusion, did not develop spores, and that animals inoculated with such cultures were made highly immune to the cultures of tetanus grown in other media. The thought suggested itself to me that if the thymus juice possesses such remarkable properties, it should be tested with a view to a possible therapeutic effect. Its administration in cases of tetanus beneath the skin could certainly do no harm, and might do good, and it might also be administered by the mouth, like the thyroid gland in myxœdema. If successful, it would prove far more valuable than the antitoxine, because so readily procurable.

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